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Ketamine Patient-Controlled Analgesia for Acute Pain in Trauma Patients: A Randomized, Active Comparator-Controlled, Blinded, Pilot Trial

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14. ABSTRACT

It is unknown whether ketamine administered via patient-controlled analgesia provides adequate analgesia in trauma patients while reducing opioid consumption in the traumatically injured patient. The objective of this study was to compare differences in breakthrough opioid consumption. It was hypothesized that ketamine patient-controlled analgesia leads to decreased opioid use and similar pain scores compared to hydromorphone patient-controlled analgesia. This was an investigator-initiated, single-center, patient- and caregiver-blinded, randomized, pilot trial conducted from 2014-2016 in a surgical intensive care unit at a level 1 trauma center. Participants were native airway trauma patients with an injury severity score of greater than 9 who were receiving patient-controlled analgesia per the primary treating team. Four subjects in the ketamine group and one subject in the hydromorphone group withdrew from the study after initiating therapy. Twenty subjects were enrolled and randomized. There was no difference in daily breakthrough opioid use (10 [0.63-19.38] mg vs. 10 [4.38-22.5] mg, P=0.55). Subjects in the ketamine group had lower median cumulative opioid use on therapy day 1 compared to the hydromorphone group (4.6 [2.5-15] mg vs. 41.8 [31.8-50] mg, P<0.001), as well as in the first 48 hours (10 [3.3-15] mg vs. 48.5 [32.1-67.5] mg, P<0.001) and first 72 hours (10 [4.2-15] mg vs. 42.5 [31.7-65.2] mg, P<0.001) of therapy. Daily median pain scores were similar between the two groups. Daily oxygen supplementation requirements were lower in the ketamine group (0.5 [0-1.5] L/min vs. 2 [0.5-3] L/min, P=0.020). Hallucinations occurred more frequently in the ketamine group, although this was not statistically significant (40% vs. 0%, P=0.090). Ketamine patient-controlled analgesia led to lower cumulative opioid consumption and improved respiratory function. Hallucinations occurred more frequently with use of ketamine. Additional studies are needed to investigate the tolerability of ketamine as an alternative to traditional opioid-based patient-controlled analgesia.

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1.0 SUMMARY

It is unknown whether ketamine administered via patient-controlled analgesia provides adequate analgesia in trauma patients while reducing opioid consumption in the traumatically injured patient. The objective of this study was to compare differences in breakthrough opioid consumption. It was hypothesized that ketamine patient-controlled analgesia leads to decreased opioid use and similar pain scores compared to hydromorphone patient-controlled analgesia. This was an investigator-initiated, single-center, patient- and caregiver-blinded, randomized, pilot trial conducted from 2014-2016 in a surgical intensive care unit at a level 1 trauma center. Participants were native airway trauma patients with an injury severity score of greater than 9 who were receiving patient-controlled analgesia per the primary treating team. Four subjects in the ketamine group and one subject in the hydromorphone group withdrew from the study after initiating therapy. Twenty subjects were enrolled and randomized. There was no difference in daily breakthrough opioid use (10 [0.63-19.38] mg vs. 10 [4.38-22.5] mg, P=0.55). Subjects in the ketamine group had lower median cumulative opioid use on therapy day 1 compared to the hydromorphone group (4.6 [2.5-15] mg vs. 41.8 [31.8-50] mg, P<0.001), as well as in the first 48 hours (10 [3.3-15] mg vs. 48.5 [32.1-67.5] mg, P<0.001) and first 72 hours (10 [4.2-15] mg vs. 42.5 [31.7-65.2] mg, P<0.001) of therapy. Daily median pain scores were similar between the two groups. Daily oxygen supplementation requirements were lower in the ketamine group (0.5 [0-1.5] L/min vs. 2 [0.5-3] L/min, P=0.020). Hallucinations occurred more frequently in the ketamine group, although this was not statistically significant (40% vs. 0%, P=0.090). Ketamine patient-controlled analgesia led to lower cumulative opioid consumption and improved respiratory function. Hallucinations occurred more frequently with use of ketamine. Additional studies are needed to investigate the tolerability of ketamine as an alternative to traditional opioid-based patient-controlled analgesia.

2.0 BACKGROUND

Opioids administered via continuous infusion, epidural infusion, intermittent intravenous push or orally, or via patient-controlled analgesia (PCA) device are the preferred analgesia for acutely injured patients [1-3]. Although opioids provide effective analgesia, untoward effects such as respiratory depression are dose-limiting, resulting in the inability to achieve adequate pain relief in some patients [4]. Opioid use has also come under scrutiny related to the current abuse epidemic in the United States. The rate of overdose deaths involving opioids has increased by 200% since the year 2000 [5]. Prescription opioid and heroin abuse led to a record high death rate due to overdose in 2014, a 14% increase from 2013 [5]. This epidemic led the Centers for Disease Control and Prevention to publish guidance on prescribing opioids for chronic pain, as chronic opioid use may lead to increased risk of opioid abuse [6]. Alternative analgesic agents may be able to help patients achieve acceptable pain control and decrease opioid use in the acute post-traumatic and post-operative setting, and curtail the need for post-acute and chronic opioid therapy.

Ketamine is an N-methyl-D-aspartate antagonist approved for use in induction and maintenance of general anesthesia. Ketamine has also been effective as a primary or adjunctive analgesic agent in post-operative patients [7-12]. Analgesia from ketamine occurs via noncompetitive blockade of glutamate, resulting in modulation of central sensation and hyperalgesia as well as direct activity on kappa, delta, and mu-1 receptors [13,14]. Potential side

effects of ketamine include hypertension, tachycardia, hallucinatory effects, and laryngospasm [7,14]. Notably, ketamine lacks the dose-limiting side effects of central nervous system and respiratory depression, key features distinguishing it from opioids [15]. As such, ketamine has gained interest as an alternative or adjunctive analgesic for acute pain management in military and civilian medicine [16].

No published studies have evaluated ketamine-only PCA in trauma patients. This pilot study aimed to assess the efficacy of ketamine PCA compared to hydromorphone PCA for baseline analgesia in native airway trauma patients with acute pain initially treated in the intensive care unit (ICU). It was hypothesized that ketamine PCA will lead to decreased breakthrough opioid use and similar pain scores compared to hydromorphone PCA in traumatically injured patients.

3.0 METHODS

3.1 Design and Oversight

This study was an investigator-initiated, single-center, randomized, patient- and caregiver-blinded, controlled study. The methodology was approved by the University of Cincinnati and the Wright-Patterson Air Force Base Institutional Review Boards. Informed consent was obtained for all subjects at the time of enrollment.

3.2 Participants

Native airway, trauma surgery patients admitted to the surgical ICU were evaluated for inclusion in the study from April 2014 through August 2016. Patients were included if they (1) were adults aged 18 years or older, (2) had a total injury severity score [17] of greater than 9, (3) were planned to receive or were using a PCA for delivery of analgesic therapy, (4) were able to effectively use a PCA device as assessed by a physician, and (5) had at least one major orthopedic injury, defined as an upper or lower extremity fracture with an Abbreviated Injury Scale of greater than or equal to 2 [17]. Due to challenges encountered with a low number of patients meeting these criteria, the inclusion criterion for orthopedic injury was removed 14 months after the trial commenced. Patients were excluded for (1) body mass index greater than 35 kg/m^2, (2) history of bipolar disorder or schizophrenia, (3) acute kidney injury (defined as serum creatinine increase of 2-3 times baseline or a glomerular filtration rate decrease of greater than 50%) [18], (4) history of chronic kidney disease, (5) history of liver failure, (6) history of heart failure or coronary artery disease, (7) opioid use as outpatient maintenance therapy, (8) need of treatment of acute withdrawal as indicated by an order for active monitoring of alcohol withdrawal by the treating physician, (9) Glasgow Coma Scale (GCS) score of less than 13 or a motor sub-score below 6 at the time of enrollment, (10) allergy to any medications used in the study (i.e., ketamine, hydromorphone, lorazepam), (11) pregnant, or (12) actively incarcerated. Cognitive function was assessed for continuation in the study by using the GCS every 6 hours. Participants were deemed cognitively impaired and ineligible for continuation if they had a GCS score of less than 13.

3.3 Treatments

Participants underwent randomization to either ketamine or hydromorphone PCA. Randomization was performed using the computerized Wichmann-Hill random number generator in blocks of 10. Participants were assigned to interventions using the random number generator by the local investigational drug services, and study personnel were not involved in randomization or treatment group assignments. Participants, caretakers, and study personnel were blinded to the treatment groups. To maintain blinding, the concentrations of ketamine and hydromorphone in the dispensed PCA syringes were set for the study so that each dosage setting (standard, minimum, or maximum) would deliver the same volume of drug whether the PCA contained ketamine or hydromorphone. Pain scores were measured using the numeric rating scale (NRS) by nurses caring for the subjects who were trained on use of the NRS. The NRS ranges from 0-10, where 0 was no pain and 10 was the worst possible pain [19]. PCA settings allowed for doses of ketamine 1.5-6 mg intravenous (IV) bolus with a lockout of 6 minutes or hydromorphone 0.1-0.4 mg IV bolus with a lockout of 6 minutes (Figure 1). No hourly limits were set, and basal infusions were reserved for subjects with persistent severe pain at highest intermittent dose and PCA mode. Both groups could receive breakthrough opioid analgesia outside of the PCA as hydromorphone 0.5 mg IV push every 2 hours as needed for pain scores with NRS of 4-6 or hydromorphone 1 mg IV push every 2 hours as needed for pain scores with NRS of 7-10. Pain scores were assessed by nursing per ICU standard of care every 2 hours using the NRS.

Lorazepam 0.5-1 mg IV was available for treatment of potential patient-reported hallucinations. If hallucinations occurred, subjects received lorazepam 0.5 mg IV. If symptoms of hallucinations did not resolve in 20 minutes, they were eligible to receive an additional 0.5 mg of lorazepam. Subjects continued randomized therapy until transfer or discharge from the ICU, or if they were transitioned off of PCA therapy to oral analgesia per the trauma physician while in the ICU.

3.4 Outcomes

The primary outcome was daily breakthrough opioid requirements between the two groups; total daily opioid requirement was assessed as a secondary outcome. Median daily pain scores measured via the NRS were also evaluated. All opioid requirements were measured in mg of IV morphine equivalents. Other outcomes included oxygen desaturation frequency (oxygen saturation less than 92%), incidence of nausea and vomiting, incidence of bowel movements, and incidence of hallucinations and delirium. Delirium was assessed by nurses caring for the patient using the Confusion Assessment Method for the ICU (CAM-ICU) score; all nurses were trained on use of the CAM-ICU score as part of standard care for patients in the unit [20]. Hospital length of stay, ICU-free days, and incidence of use of opioids on first follow-up appointment post-hospital discharge were also assessed.

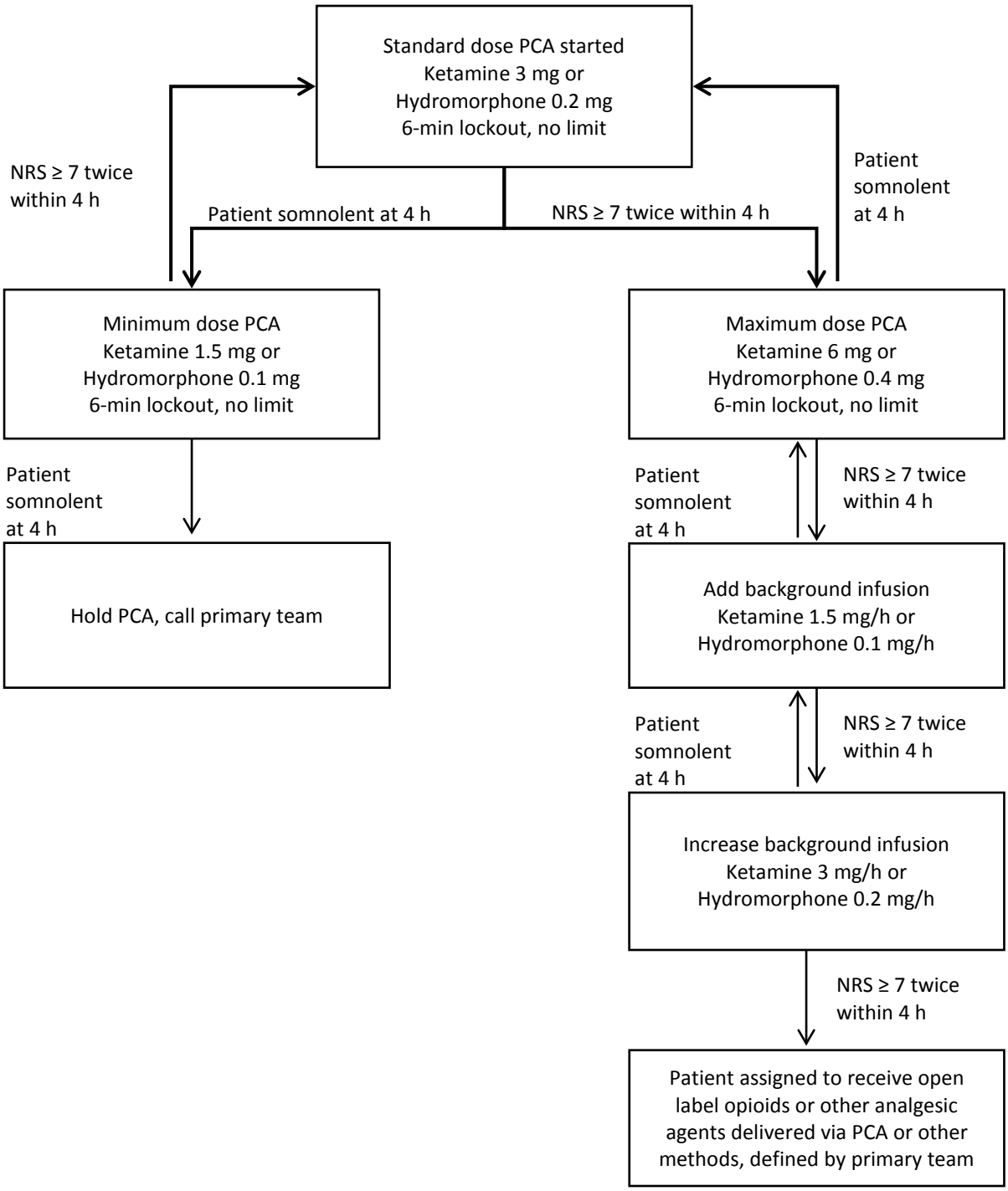

Figure 1. Flow diagram of randomized treatment.

3.5 Statistical Analysis

Data were analyzed using SAS version 9.4 (SAS Institute; Cary, NC). An intention-to-treat model was used for data analysis. Nominal data were reported using frequencies of occurrence and proportions as appropriate. Ordinal and continuous data were reported using medians and interquartile ranges (IQRs). Hypothesis testing was two-sided and was performed using the Fisher's exact test or chi square test as appropriate based on sample size. Ordinal and non-parametric continuous data were compared using a Wilcoxon rank-sum test. A *P*-value of less than 0.05 was considered statistically significant.

Given the pilot nature of this study, it was planned to enroll a total of 30 patients (15 in ketamine group and 15 in hydromorphone group). This sample size would provide 80% power with an alpha level of 0.05 to detect at least 10 ± 10 mg absolute difference in total daily breakthrough IV morphine equivalents between groups.

4.0 RESULTS

4.1 Participants

Due to unanticipated barriers to enrollment, including a lower than expected number of eligible patients meeting inclusion criteria, study enrollment was suspended before reaching the planned 30 patients. A total of 330 patients met inclusion criteria for enrollment, and 266 patients met one or more exclusion criteria (Figure 2). Forty-five patients met inclusion criteria, but were excluded for various reasons outside of exclusion criteria (Figure 2). Twenty participants were enrolled in the study, underwent randomization, and were included in the intention-to-treat analysis. Four subjects in the ketamine group withdrew from the study after initiating treatment (study days 1, 4, 1, and 3, respectively), and one subject in the hydromorphone group withdrew from the study after initiating treatment (study day 1) (*P*=0.30). No statistically significant differences in demographics were noted between the ketamine group and the hydromorphone group (Table 1).

Participants enrolled in the study largely remained on the standard starting dose of PCA therapy, with the exception of the following four subjects. Two participants in the hydromorphone group moved to the maximum dose because of uncontrolled pain, one after 17 hours of therapy and one after 24 hours of therapy. One participant in each group moved to the minimum dose of PCA therapy due to excessive somnolence. There were no statistically significant differences in transition of PCA doses between the two groups.

4.2 Outcomes

Opioid use in the two groups is listed in Table 2. There was no difference in breakthrough opioid use between the ketamine and hydromorphone groups at any time point in the study or in daily median breakthrough opioid use over the course of treatment (10 mg [0.63-19.38 mg] vs. 10 mg [4.38-22.5 mg], *P*=0.55). Subjects received a similar median number of breakthrough opioid doses per day between the two groups (1.9 [1-2.5] doses in the ketamine group vs. 1.5 [0.5-2.7] doses in the hydromorphone group, *P*=0.85). Subjects in the ketamine group had a lower median total opioid use on day 1 of therapy compared to the hydromorphone group (4.6 mg vs. 41.8 mg, *P*<0.001). Total opioid use was also significantly lower in the

ketamine group in the first 48 hours (10 mg vs. 48.5 mg, $P<0.001$) and first 72 hours (10 mg vs. 42.5 mg, $P<0.001$) of the study. Additionally, the total amount of opioid that a subject received per day of therapy was significantly lower in the ketamine group compared to the hydromorphone group (9.2 mg vs. 45 mg, $P=0.020$). NRS values were not statistically different between the two groups for each day of therapy (Table 2). There were no differences noted in the adjunctive analgesic therapies used between the two groups (Table 3).

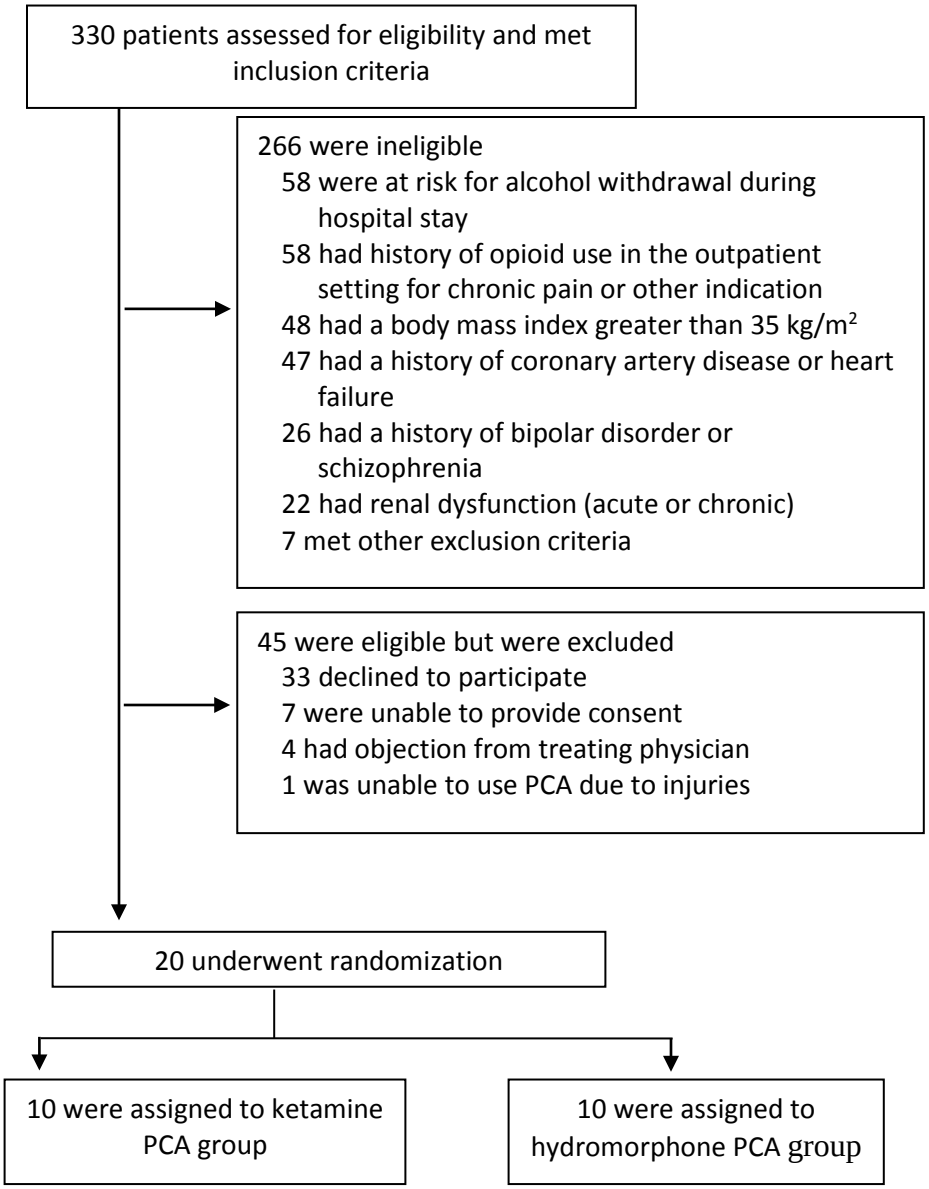

Figure 2. Flow diagram of participant screening and enrollment.

Table 1. Baseline Demographics[a]

Clinical Value	Ketamine PCA Group (n=10)	Hydromorphone PCA Group (n=10)
Age, median (IQR), yr	39 (28-47)	26 (22-30)
Sex, no. male (%)	7 (70%)	9 (90%)
Race, no. (%)		
White	7 (70%)	8 (80%)
Black	2 (20%)	2 (20%)
Hispanic	1 (10%)	0 (0%)
Body mass index, median (IQR), kg/m^2	27 (23.8-29)	26.5 (21.7-29)
Total injury severity score, median (IQR)	29 (22-33)	28 (26-29)
Abbreviated Injury Scale (AIS) general, median (IQR)	1 (1-1)	1 (1-1)
AIS head and neck, median (IQR)	1 (0-2)	1.5 (1-3)
AIS chest, median (IQR)	3 (2-3)	3 (3-3)
AIS abdomen, median (IQR)	4 (3-4)	2 (0-4)
AIS extremities, median (IQR)	2.5 (0-3)	2 (2-3)
Past medical history, no. (%)		
Chronic pain not requiring opioids	0 (0%)	1 (10%)
Anxiety disorder	0 (0%)	1 (10%)
Depression	1 (10%)	0 (0%)
Selective serotonin receptor antagonist use	1 (10%)	0 (0%)
Mechanism, no. (%)		
Blunt trauma	10 (100%)	9 (90%)
Penetrating trauma	0 (0%)	1 (10%)
Days on study drug, median (IQR)	1.58 (0.85-2.19)	1.94 (1-2.8)
Hours on study drug, median (IQR)	38 (20.5-52.5)	46.5 (24-68)
Patients >24 h on study drug, no. (%)	6 (60%)	6 (60%)
Withdrew from study after therapy initiation, no. (%)	4 (40%)	1 (10%)

[a]No statistically significant differences ($P<0.05$) noted between groups.

Table 2. Breakthrough Opioid Use, Cumulative Opioid Use, and Pain Scores

Outcome	Ketamine Group (n=10)	Hydromorphone Group (n=10)	*P*-Value
Breakthrough opioids day 1[a], median (IQR)	4.6 (2.5-15)	5 (2.5-15)	1.00
Breakthrough opioids day 2[a], median (IQR)	12.5 (10-15)	10 (0-15)	0.36
Breakthrough opioids day 3[a], median (IQR)	12.5 (10-25)	12.5 (0-15)	0.65
Total opioid use day 1[a], median (IQR)	4.6 (2.5-15)	41.8 (31.8-50)	<0.001
Total opioid use day 2[a], median (IQR)	12.5 (10-15)	57.5 (39.5-87)	0.09
Total opioid use day 3[a], median (IQR)	12.5 (10-25)	33 (25-42.5)	0.10
NRS scores day 1, median (IQR)	6.5 (3-7)	5 (3-5.5)	0.30
NRS scores day 2, median (IQR)	5.5 (4-8)	4.25 (1-6)	0.26
NRS scores day 3, median (IQR)	7 (6-8)	3.5 (3-6)	0.13
Median NRS score for entire treatment course, (IQR)	6.3 (4-7.5)	5.3 (3-6.8)	0.19

[a]mg morphine equivalents.

Table 3. Treatment Effects and Adjunctive Therapies

Effect/Therapy	Ketamine Group (n=10)	Hydromorphone Group (n=10)	*P*-Value
Hallucination, no. (%)	4 (40%)	0 (0%)	0.09
ICU delirium, no. (%)	1 (10%)	0 (0%)	1.00
Nausea/vomiting, no. (%)	5 (50%)	3 (30%)	0.65
Pruritis, no. (%)	0 (0%)	4 (40%)	0.09
Oxygen desaturation events, no. (%)	2 (20%)	5 (50%)	0.35
Spontaneous bowel movement, no. (%)	1 (10%)	5 (50%)	0.14
Acetaminophen, no. (%)	9 (90%)	6 (60%)	0.30
Transdermal lidocaine, no. (%)	4 (40%)	4 (40%)	1.00
Gabapentin, no. (%)	0 (0%)	1 (10%)	1.00
Epidural, no. (%)	1 (10%)	1 (10%)	1.00
Lorazepam, no. (%)	3 (30%)	2 (20%)	1.00
Haloperidol, no. (%)	0 (0%)	0 (0%)	1.00
Quetiapine, no. (%)	1 (10%)	0 (0%)	1.00
Vasoactive medications, no. (%)	0 (0%)	0 (0%)	1.00
Antihypertensive medications, no. (%)	1 (10%)	0 (0%)	1.00

Hospital length of stay in the ketamine versus hydromorphone group (7 [6-19] days vs. 9 [7-16] days, *P*=0.68) and ICU-free days in the ketamine versus hydromorphone group (27 [26-28] vs. 26 [22-28] days, *P*=0.86) were similar. All participants who had a documented follow-up visit in the trauma clinic after discharge from the hospital (six subjects in the ketamine group and nine subjects in the hydromorphone group) reported continued use of opioid analgesics.

4.3 Treatment Effects

More participants in the ketamine group experienced hallucinations compared to the hydromorphone group, but this did not reach statistical significance (Table 3). There was no difference in the number of lorazepam doses administered between the two groups for management of hallucinations or other indications (Table 3). There was no difference in the incidence of ICU delirium. There were also no differences in the rates of nausea and vomiting, pruritus, oxygen desaturation events, and spontaneous bowel movements between the two groups (Table 3). Daily oxygen supplementation requirements, however, were lower in the ketamine PCA group compared to the hydromorphone PCA group (0.5 [0-1.5] L/min vs. 2 [0.5-3] L/min, *P*=0.020).

5.0 DISCUSSION

The objective of this pilot study was to compare opioid use and pain scores between native airway trauma patients in the ICU receiving ketamine PCA or hydromorphone PCA. Breakthrough opioid use was not found to be different between the two groups, but cumulative opioid use was lower in the ketamine PCA group compared to the hydromorphone PCA group.

Higher cumulative opioid use in the hydromorphone PCA group was not unexpected, as those patients were receiving opioid through their PCA and the ketamine PCA group was not. Despite ketamine patients receiving significantly less total opioid, pain scores were not significantly different between the two groups. Lengths of stay in the ICU and hospital were not different between the two groups. These results indicate that ketamine delivered via a PCA is a useful adjunctive agent for acute analgesia for trauma patients in the ICU setting.

Consequences of uncontrolled pain in critically ill post-operative patients include exhaustion due to lack of sleep, disorientation, agitation, stress response, and post-traumatic stress disorder [1,2]. Patients recall pain as a major source of stress during their ICU stays [1]. Use of opioid medications for the treatment of acute pain in critically ill trauma patients is standard of care, but the adverse effect profile of these agents may limit optimal efficacy, particularly hypotension, bradycardia, central nervous system depression, decreased gastrointestinal motility, and respiratory depression [1]. Notably, the ketamine group in this pilot study had lower oxygen supplementation requirements compared to the hydromorphone group, which could be an indicator of improved respiratory function in the ketamine group and lower rates of respiratory depression.

Administering analgesia via a PCA device allows patients to deliver analgesic doses when required and can prevent overuse by implementing a lockout for dose administration, allowing baseline analgesia to be achieved without over-sedation or undertreatment [3]. The primary mechanism of action for ketamine is through N-methyl-D-aspartate antagonism, although the drug may exhibit additional receptor activity including opioid receptor antagonism and gamma aminobutyric acid antagonism [21]. When administered intravenously, ketamine has an immediate onset of action, with a dose-dependent duration of action of 5-20 minutes [21]. This short onset and duration of action may be advantageous for PCA. The adverse effect profile of ketamine differs from opioids that are traditionally used by PCA. Ketamine is less likely to depress respiratory protective reflexes and to cause respiratory depression compared to opioids. Ketamine can cause both excitatory and depressive effects in the central nervous system, whereas opioids cause only depressive effects. Ketamine may cause hallucinations or other psycho-mimetic reactions, and these anticipated effects can be treated with use of intermittent benzodiazepines [22]. Finally, the effects of ketamine on the cardiovascular system differ from opioids and other sedative agents through inhibiting catecholamine reuptake leading to increased heart rate and blood pressure. Conversely, opioid use may lead to reduced heart rate and blood pressure [21].

Studies have shown that ketamine provides analgesia when administered at sub-dissociative doses (bolus doses of less than 500 μg/kg) [5]. One trial evaluated the analgesic effects of post-operative small-dose ketamine continuous infusion of 2 μg/kg/min compared to placebo on morphine consumption in 101 patients receiving morphine PCA following major abdominal surgery. Cumulative 4-hour morphine doses were significantly lower in the ketamine group than the placebo group. Mean morphine consumption over 48 hours was also significantly lower in the ketamine group compared to the placebo group (58 ± 35 mg vs. 80 ± 37 mg, $P<0.05$). The mean ketamine consumption over 48 hours was 367 ± 37 mg. No significant differences in adverse effects between the two groups were observed [23]. Although supportive of ketamine as an adjunctive therapy, use as a continuous infusion may have limited practicality across inpatient environments.

Other studies have evaluated the combination of opioids plus ketamine PCA compared to opioids alone [8,24]. These studies have wide variability in bolus PCA doses, lockouts, and

limits on the PCA pumps. Many trials have shown improved pain control and opioid-sparing effects of this strategy with no differences in adverse events [9-12]. However, other studies show no advantage to the combination of morphine and ketamine in PCAs compared to morphine alone [25,26] One case report describes the use of ketamine alone in a PCA device for a patient experiencing intractable central pain. The settings on the PCA device were a basal rate of ketamine delivered at 2.7 mg/h with a 2.7-mg bolus demand dose. The lockout was 15 minutes with no 4-hour limit. Ketamine was a viable treatment option to control pain in this report [27]. From these studies, intermittent ketamine PCA doses between 2-5 mg have been suggested [28].

The major limitation of the current study was unforeseen low enrollment rate. Many patients were ineligible because they met exclusion criteria set to mitigate potential confounders given the pilot nature of the trial. Also, a higher than anticipated number of patients declined to participate in the study after being deemed eligible. Additionally, there was a relatively high withdrawal rate from the study. Five patients withdrew after receiving treatment: three due to experiencing the effects of hallucinations, a well-known effect of ketamine, and two due to a perception of inadequate analgesia. Although “as needed” lorazepam was available for intermittent treatment of hallucinations, scheduled low-dose benzodiazepine may have better addressed this adverse effect. The decision to not use a scheduled frequency for lorazepam in this study was to avoid additional risk in the hydromorphone subjects given the well-known additive adverse effects of combination therapy. The study was stopped early by the investigators due to the high dropout rate and challenges with enrollment, which may cause the study to be underpowered to find statistically significant differences where they exist. Future investigations of ketamine-only PCA should note these challenges in awake patients receiving randomized therapy.

6.0 CONCLUSION

Use of a ketamine-only PCA led to lower total opioid consumption in native airway trauma patients in the ICU. Respiratory function was improved in the ketamine group, but hallucinations occurred more frequently with use of a ketamine PCA compared to hydromorphone PCA. Due to low enrollment and study withdrawals, additional studies are needed to investigate the tolerability of ketamine used alone in PCA.

7.0 REFERENCES

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LIST OF ABBREVIATIONS AND ACRONYMS

AIS	Abbreviated Injury Scale
CAM-ICU	Confusion Assessment Method for the ICU
GCS	Glasgow Coma Scale
ICU	intensive care unit
IQR	interquartile range
IV	intravenous
NRS	numeric rating scale
PCA	patient-controlled analgesia